2016-12-05

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Int J Cancer. 2017 Feb 1;140(3):581-590.
http://doi.org/10.1002/ijc.30476
http://hdl.handle.net/10616/45418

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Differences in survival for patients with familial and sporadic cancer

Authors:

Myeongjee Lee[1,2*] , Marie Reilly[1] , Linda Sofie Lindström[3,4] , Kamila Czene[1]

Affiliations:

1- Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

2- Department of Occupational and Environmental Medicine, School of Medicine, Ewha Womans University, Seoul, South Korea

3- Department of Biosciences and Nutrition, Karolinska Institutet and University Hospital, Stockholm, Sweden

4- University of California at San Francisco (UCSF), Department of Surgery, San Francisco, California, USA

* Correspondence to:

Dr. Myeongjee Lee

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet,

Nobels väg 12A, Stockholm, 171 77, Sweden

Phone: +46-8- 524 823 27; Fax: +46-8-314975; Email: myeongjee.lee@ki.se

Key words: common cancers, population-based, survival, family history, histology

Abbreviations: HR: hazard ratio; CI: confidence interval; ICD7: the seventh revision of the International Classification of Disease; PAD: patho-anatomic diagnosis; SNOMED: Systematized Nomenclature of Human Medicine; FIGO: The International Federation of Gynecology and Obstetrics; TNM: tumor size (T), lymph nodal involvement (N) and metastatic (M) status; ORs: odds ratios; PSA: Prostate-specific antigen

The appropriate article category: Cancer Epidemiology

The novelty and impact of the work: This study based on nationwide registers provides evidence that family history of cancer is a prognostic factor for cancers at some sites and histological type of cancer also has further prognostic value. Patients with familial breast and prostate cancer have better survival. The poor survival for patients with familial ovarian cancer is multifactorial.

Abstract

Family history of cancer is a well-known risk factor but the role of family history in survival is less clear. The aim of this study was to investigate the association between family history and cancer survival for the common cancers in Sweden.

Using the Swedish population-based registers, patients diagnosed with the most common cancers were followed for cancer-specific death during 1991-2010. We used multivariate proportional hazards (Cox) regression models to contrast the survival of patients with a family history of cancer (individuals whose parent or sibling had a concordant cancer) to the survival of patients without a family history.

Family history of cancer had a modest protective effect on survival for breast cancer (hazard ratio (HR) = 0.88, 95% confidence interval (95% CI) = 0.81 to 0.96) and prostate cancer (HR = 0.82, 95% CI = 0.75 to 0.90). In contrast, family history of cancer was associated with worse survival for nervous system cancers (HR = 1.24, 95% CI = 1.05 to 1.47) and ovarian cancer (HR = 1.20, 95% CI = 1.01 to 1.43). Furthermore, the poorer survival for ovarian cancer was consistent with a higher FIGO stage and a greater proportion of more aggressive tumors of the serous type.

The better survival for patients with a family history of breast and prostate cancer may be due to medical surveillance of family members. The poor survival for ovarian cancer patients with an affected mother or sister is multifactorial, suggesting that these cancers are more aggressive than their sporadic counterparts.

Introduction

Family history of cancer is considered an important risk factor and extensive work has been done to understand the risk associated with a family history for different cancers.[1-4] In addition to the risk of developing cancer, family history of cancer survival has been suggested to be important for the cancer survival of a newly diagnosed individual.[5]

We have previously shown that survival from cancer is in part inherited.[6, 7] One potential explanation for the association of survival among family members could be that relatives are at higher risk to develop a cancer tumor of predefined biology. Indeed, it has been shown that carriers of mutations in high-risk genes are more likely to develop a specific subtype of cancer.[8] It is also possible that the survival concordance in families is related to the inheritance of host characteristics for instance affecting the ability to mount an effective anti-tumoral immune response or respond to cancer therapy.[9] Furthermore, shared characteristics such as health-seeking behavior, treatment choices and life-style, are likely to be important for explaining the survival similarities among relatives.[10] Although we and others have investigated the concordance of survival in families, much less is known about differences in survival for patients with a family history of cancer as compared to patients without a family history (sporadic cancer).[11, 12]

Therefore our aim in this study was to determine whether patients with a family history of cancer have a differential survival as compared to patients without a family history of cancer. Using Swedish population-based registers, we studied familial cancers with sufficient sample sizes to consider the kinship of affected relatives. For those cancers with any significant association, we explored in depth the effect of age at diagnosis and the histological tumor type on survival differences, and examined the association between stage information at diagnosis and family history of cancer.

Materials and Methods

Data Sources

The data for this study is from a linkage of several Swedish population- based registers that has been described previously.[4] Individuals included in this study are all recorded in the Swedish Cancer Register with a first primary malignancy from January 1, 1991 to December 31, 2009. To obtain the exposure information (i.e. family history of cancer), these patients are linked to their first degree relatives in the Swedish Multi-Generation Register. The Swedish Multi-Generation Register records the biological parents for all children born in Sweden from 1932 who were alive in 1961, with essentially complete parental information from 1991.[13] The cancer diagnoses of these family members were obtained from the Swedish Cancer Register (which was established in 1958 [14]). We selected two cohorts of children for analysis: The first cohort included individuals with both biological parents identified (to investigate the effect of parental cancer history on survival), and the second cohort included individuals with at least one sibling (to investigate sibling effects). We followed these individuals for cancer-specific death in the Cause of Death Register which was available up to the end of 2010 with a reported accuracy of 96%.[6] Some additional information for censoring (date of emigration) was obtained from the Total Population Register and socioeconomic status was obtained from the census files from 1960, 1970, 1980, 1990.

Cancers Studied

The Swedish Cancer Register records all malignant cancers diagnosed since 1958 according to the seventh revision of the International Classification of Disease (ICD7). We included cancers that provided a sufficient sample size to address our hypotheses, namely stomach (ICD7=151), colorectal (ICD7=153-4), lung (ICD7=162-3), breast (ICD7=170), ovarian (ICD7=175), prostate (ICD7=177), kidney (ICD7=180), bladder (ICD7=181), melanoma (ICD7=190), nervous system (ICD7=193), non-Hodgkin's lymphoma (ICD7=200, 202) and leukemia (ICD7=204-209). [15] For cancer of the nervous system and leukemia, we only included patients who were at least 15 years old

at primary tumor diagnosis because types of childhood cancers are often different from the types of adult cancers.[16, 17]

Variables

In addition to the ICD codes, the Swedish Cancer Register records information on histopathological type and patho-anatomic diagnosis (PAD), according to WHO/HS/CANC/24.1. The information on histological type enables cancers to be classified into main subgroups, such as adenocarcinoma and squamous cell carcinoma.[1] Detailed morphologic information, the Systematized Nomenclature of Human Medicine histology (SNOMED, http://snomed.org), was available from 1993 according to ICD-O/2 (2nd Edition. WHO Geneva 1990) and from 2005 according to ICD-O/3 (3rd Edition WHO Geneva 2000).[18] Stage information was collected since 2004 according to FIGO (The International Federation of Gynecology and Obstetrics, http://www.figo.org) for gynecological tumors or TNM stage (tumor size (T), lymph nodal involvement (N) and metastatic (M) status) for other tumors [19] except those of the nervous-system, lymphomas and leukemia.[18, 20] The completeness of cancer registration (with cytological or histological verification) is considered high.[18]

Our outcome variable, cancer-specific death, was defined by the underlying cause of death in the Swedish Cause of Death Register which is recorded using ICD codes. Our main exposure, family history of cancer, was defined as having at least one parent or sibling with a record of a diagnosis of a concordant cancer. The region in which the cancer diagnosis was registered, which was available from the Swedish Cancer Register, was classified as six medical regions.[18] The socioeconomic status from the Census data was grouped into five categories; blue-collar workers, white collar workers, self-employed workers, farmers and unclassified.

Statistical Methods

Our main analyses compared the cancer-specific survival for up to 5-years after diagnosis for patients with and without a family history of cancer. Using multivariate proportional hazards (Cox) regression models, we estimated the hazard ratio (HR) of cancer-specific death for

patients with a family history of the specific cancer as compared to patients without a family history (the reference group). In these analyses we adjusted for gender, age and calendar year of diagnosis, socioeconomic status and the region where the individual was diagnosed with cancer. Survival time was defined as the elapsed time from the date of cancer diagnosis until the date of cancer-specific death or censoring (death due to other causes, emigration, end of study, or 31 December 2010, whichever occurred first) within 5 years of diagnosis. If there was no other censoring event, patients were censored at 5 years after diagnosis. We also conducted stratified analyses by type of relationship (affected parent or sibling), age at diagnosis (classified as above or below the median) and by the specific histological type of cancer (subtype for leukemia).

Since any difference in survival between patients with a family history and patients without a family history might be due to differences in histology distribution or differential survival within histological type, we compared the distribution of the histological type in the familial and sporadic cases (for the period from 1993 when SNOMED codes became available) and estimated the mortality in the five years following diagnosis for each histological type. Leukemia subtypes defined using the fourth digit of the ICD7 code[3] were analyzed for the same period. The distribution of tumor histological type in patients with or without a family history was compared using the Pearson Chi-square test. For cancers with significant results from the Pearson Chi-square test, post-hoc tests contrasting each histological type against the others were conducted and Bonferroni corrections used for p-value adjustment.

In addition, we investigated whether there is a differential survival for patients with a family history compared to patients without a family history of cancer associated with stage (TNM stage at cancer diagnosis for stomach, breast and prostate cancers, or with FIGO stage for ovarian cancer). For this analysis, we performed a logistic regression with stage information as outcome, family cancer history as the main exposure, and adjusting for sex, age at diagnosis, year of diagnosis, socioeconomic status and region. We present odds ratios (ORs) that provide a measure of the frequency of combined higher categories of stage relative to the lowest category in patients with a family history compared with patients without a family history of concordant cancer (i.e., T2-T4 *vs* T1). Where there were any significant differences, we investigated each of the higher categories

separately. These analyses were conducted for the period from 2004 when stage information was available.

All data preparation and analyses were performed using the SAS statistical package, version 9.4 (SAS Institute, Cary NC).[21]

Results

The study population for each cancer investigated is described in Table 1, including the total number of patients diagnosed with the cancer, number of cancer-specific deaths and median age at diagnosis.

In Table 2, we present the hazard ratios of cancer-specific death within five years for cancer patients with a family history compared to cancer patients without a family history. For breast cancer, prostate cancer and leukemia, we found that a concordant family cancer history played a protective role for cancer survival in patients: hazard ratio (HR) was 0.88, (95% confidence interval (CI) = 0.81 to 0.96) for breast cancer, HR = 0.82, (95% CI = 0.75 to 0.90) for prostate cancer, and HR = 0.70, (95% CI = 0.54 to 0.92) for leukemia. In contrast, familial cancer patients had worse survival for patients with ovarian cancer and nervous system cancer: HR = 1.20, (95% CI = 1.01 to 1.43) and HR = 1.24, (95% CI = 1.05 to 1.47), respectively.

For the six cancers that had any significant association, in Table 2, we further investigated the role of age, kinship, and histological type in the differential cancer survival. For breast and prostate cancer and leukemia, the protective effect was strongest in younger patients (Table 3, last column). Familial ovarian cancer patients who were diagnosed at younger ages had consistently significantly higher risk of death in the 5 years after the cancer diagnosis than patients with sporadic cancer, HR = 1.44, (95% CI = 1.14 to 1.81) and the relative risk was highest when a sister was affected, HR = 1.75, (95% CI = 1.23 to 2.49).

Comparing the distribution of the histological type between familial and sporadic cancers, we found significant differences for breast cancer, ovarian cancer and leukemia (Table 4, last

five columns). Lobular breast cancer, which has a lower mortality rate than the more common ductal type, was slightly more common in breast cancer patients with a family history than in patients without a family history, 14.1% versus 12.8% (p = 0.015). Serous ovarian cancer was more often detected in familial cancer patients (54.8% for familial cancer patients *vs.* 43.3% for sporadic cancer patients) (p = 0.001) and the very high mortality rate for serous ovarian cancer thus contributes to the higher risk of cancer death in familial ovarian cancer patients. Lymphatic leukemia was more common among familial cases of adult leukemia ($p < 0.001$) and the lower mortality rate for this subtype thus explains in part the protective effect of family history.

The associations between family cancer history and survival for each specific histological type of cancer are presented in Table 5. For ductal breast cancer and adenocarcinoma of the stomach and prostate, patients with a family history had better survival than patients without a family history with the same histological type (HR ranging from 0.80 to 0.86). However, for mucinous ovarian cancer, patients whose mother or sister was diagnosed with the same cancer had twice the risk of death compared to sporadic cancer patients, HR = 2.09, (95% CI = 1.09 to 3.98). For nervous system cancer, patients with a family history had much worse survival than patients without a family history when their cancer was gliomas of uncertain origin, HR = 2.78, (95% CI = 1.16 to 6.65) or classified as 'other' histological type, HR = 2.35, (95% CI = 1.12 to 4.93).

Finally, we explored the stage information at diagnosis in patients with a family history and patients without a family history of concordant cancer (Table 6). Prostate cancer patients with a family history were less likely to be diagnosed with tumors of larger size/extent compared to patients without a family history (p=0.006). Family cancer history of prostate cancer was associated with a reduction of 11% in the odds of tumors diagnosed in the T3 category (OR = 0.89, 95% CI = 0.81 to 0.97, T3 vs T1), consistent with the protective effect we observed for family history. We observed a large and significant increase in the odds of higher FIGO stages *vs* the lowest stage (stage I) for ovarian cancer OR = 2.70, (95% CI = 1.46 to 4.97) and a significant OR for each of stages II, III and IV: OR = 2.79, (95% CI = 1.21 to 6.40) for stage II, OR = 2.52, (95% CI = 1.33 to 4.79) for stage III, and OR = 3.22, (95% CI = 1.52 to 6.79) for stage IV, respectively.

Although there was no significant difference in TNM stage in breast cancer patients with and without a family history of breast cancer, we implemented additional analysis for the two main histological types (ductal and lobular) which had sufficient number of cases (Supplementary Table 1). For ductal breast cancer, patients with family history of breast cancer tended to be diagnosed with smaller tumor size (p=0.01) with an OR of 0.88, (95% CI = 0.78 to 0.98) for T2-T4 *vs* T1. For lobular breast cancer, a family cancer history of breast cancer was associated with an increase in the odds of positive nodal involvement *vs.* negative nodal involvement: OR=1.33, (95% CI = 1.02 to 1.73).

Discussion

We have demonstrated a different role for family history of cancer in cancer survival for 5 years after diagnosis depending on the cancer site; a protective effect for stomach cancer, breast cancer, prostate cancer and leukemia but a poorer survival for ovarian cancer and nervous system cancers. No associations were found for lung cancer, kidney cancer, bladder cancer, melanoma or non-Hodgkin's lymphoma. The potential explanations for the differential survival varied with cancer site: earlier stage at diagnosis for familial prostate cancer, a higher proportion of a less aggressive subtype for familial leukemia and differential survival within histological type of nervous system cancers. For ovarian cancer, the much poorer survival for familial cancers had a contribution from all of these factors, reflecting highly aggressive tumors in familial cases and suggesting that these may have a distinct genetic profile that has not yet been characterized.

Since each cancer has a different prognosis, we chose to focus on the 5-year interval following diagnosis, as this is common in cancer recurrence and survivorship studies.[22] However, breast cancer and prostate cancer have much lower mortality than the other cancers studied (Table 4) so that a longer period of follow-up would be more appropriate. We repeated our comparison of familial and non-familial breast and prostate cancer using all available follow-up time and none of these analyses changed our current conclusions. (Supplementary Table 2) In sensitivity analyses, we compared cancer-specific overall survival after diagnosis for familial cancer patients to the cancer-

specific overall survival of sporadic cancer patients and also implemented our analyses on a wider cohort of cancer patients diagnosed during 1961-2009, and these analyses did not change our current conclusion (data not shown).

For most common cancers, few systematic and detailed investigations of survival differences between familial and sporadic cancer have been done previously, but our findings are consistent with earlier studies on familial survival for stomach cancer, ovarian cancer and bladder cancer.[11, 12, 23, 24] Recently, Kharazmi *et al.* (2016) compared survival in familial and non-familial breast cancer by age and stage at diagnosis using the Swedish Family-Cancer Database. [25] They found no evidence for familial breast cancer diagnosis at an earlier TNM stage compared to sporadic cases, which is in line with our findings in Table 6. However, we did find evidence that for ductal breast cancer, familial cases are diagnosed with smaller tumor size, consistent with the survival advantage we observed. In addition, our histology-specific mortality rates were largely in agreement with the literature on cancer survival, with poorer survival for ductal breast cancer,[26, 27] signet ring stomach cancer,[28] non-adenocarcinoma prostate cancer,[29] serous ovarian cancer,[11] astrocytic nervous system cancers and gliomas of uncertain origin,[30] and a significantly better survival for lymphatic leukemia than for other subtypes.[31]

A small survival benefit was seen in patients with a family history of breast cancer in our study, which was more pronounced if the affected relative was a sister. Thus, even with nationwide mammographic screening since the 1990s in Sweden,[32] this finding suggests earlier detection due to increased awareness and positive medical surveillance in women with a family history of breast cancer. Such lead time bias was apparent for ductal breast cancer, the most common histological type, where we found that patients with a family history were more often diagnosed with smaller tumors. In contrast, for lobular breast cancer, which accounted for approximately 13% of all breast cancers and is harder to detect by mammography,[27] familial cases tended to have larger tumor sizes and cases were at increased risk to be diagnosed with lymph node positive tumors. While this suggests a more aggressive disease in familial lobular breast cancer, there was no evidence of a higher cancer-specific mortality in familial cases. A possible interpretation is that familial lobular cancer is

somehow different than sporadic and that more research of this specific histological type is needed, in particular since it is known to be hard to detect through mammographic screening.

Even though some early studies suggested that familial disease may have a more aggressive course in prostate cancer, the overall data suggest that the survival of patients with a family history is not essentially different from that of patients without a family history of prostate cancer.[33-35] Prostate-specific antigen (PSA) testing has been suggested to be one of the reasons for the inconsistent results.[33] PSA testing was introduced in Sweden in the mid-1990s with a rise in incidence reported after this time.[36] In a previous study, we reported a significantly increased risk of prostate cancer diagnosis shortly after a diagnosis in a brother in the calendar period after the introduction of PSA testing.[4] Since prostate cancer has a long lead time[37], this suggests that sons or brothers of prostate cancer patients may be more likely to seek medical attention and thus have higher probability of early detection due to the opportunistic screening, which in turn will contribute to a protective effect of family history such as we observed. We also found a significantly reduced risk of familial prostate cancer patients being diagnosed with a larger tumor, again reflecting lead-time bias in these patients.

The protective effect of family history for leukemia is consistent with the preponderance of lymphatic leukemia, which is well known to be more familial than other subtypes,[38-40] and the better survival of this subtype.

Our findings of a poor survival in women with a family history of ovarian cancer are in agreement with previous studies.[11, 23] We found familial ovarian cancer patients who were diagnosed before 55 years of age had consistently significantly higher risk of death in the 5 years after the cancer diagnosis compared to patients with sporadic cancer. This might be due to germline mutations relevant to ovarian cancer.[41] A contributing factor to the differences in survival for familial and sporadic cases of ovarian cancer is the distribution of histological types. In agreement with previous studies,[42] we found serous ovarian cancer to be more familial than other histological types and BRCA1 or BRCA2 carriers are more likely to have this histology.[43, 44] Since the survival is poorer for

serous histology than for other subtypes,[11] this results in a higher risk of cancer death for familial cancers. However, for patients with serous ovarian cancer we found no evidence that family cancer history had any further effect on survival, in agreement with previous reports indicating that women with BRCA1/BRCA2 mutations can even have a survival advantage.[43, 44] On the contrary, patients with familial mucinous ovarian cancer, who are not BRCA1 or BRCA2 mutation carriers,[44] have increased risk of death in our data, possibly suggesting germline mutations associated with prognosis or therapy response. Since a reasonable proportion of ovarian cancers are mucinous, the differential survival for this histology type adds further to the risk of death associated with family history. We also observed that ovarian cancer patients with a family history were more likely to be diagnosed with tumor of higher FIGO stage than patients without a family history. In the absence of any available diagnostic test to date with sufficient accuracy to identify early-stage ovarian cancer,[45] this is again consistent with more aggressive tumors in familial cases.

For nervous system cancers, we found astrocytic histology to have the worst mortality rates, followed by gliomas of uncertain origin, findings that are in agreement with other studies.[30] Although the distribution of histological types was similar among patients with a family history and patients without a family history, the familial cancer patients with gliomas of uncertain origin had poorer survival than sporadic cancer patients.

Strengths of this study include the use of Swedish population-based registers that have almost complete ascertainment of cancer cases providing an unbiased assessment of family history and long follow-up. The Swedish national cancer register has been validated and shown to have a high level of completeness (98%).[18] In addition, the availability of information on detailed histological type and stage enables us to explore these factors in an effort to elucidate any noted differences in survival for familial and sporadic cancer patients.

Despite the positive aspects of our study, the study also has several limitations. First, the Swedish Cancer Register contains no information on treatment, which might affect survival. However, it is unlikely that differential treatments are provided to familial and non-familial cancer

patients in Sweden, where the public health system provides similar treatment to all patients according to general guidelines.[25] Nonetheless, regional differences in treatment might exist. Therefore, we adjusted all our models for the region where the patient was diagnosed. Changes in diagnosis and treatment protocols over time might also affect survival, and in an effort to adjust for these changes we also adjusted our models for calendar year of cancer diagnosis. Another limitation of our study is that there is no information on important risk factors such as obesity, alcohol consumption, and smoking.

In conclusion, our findings provide evidence that family history of cancer is a prognostic factor for cancers at some sites and histological type of cancer also has further prognostic value. Further work is needed to understand the role of screening in family members. The strong association of more aggressive ovarian cancers in sisters and daughters of patients diagnosed with ovarian cancer may be informative for genetic counseling and help to guide further molecular or genetic investigations.

Acknowledgments

This work was supported by the Swedish Research Council (grant numbers: 80748301, 2014-2271 and 521-2014-2057), the Swedish Cancer Society [Cancerfonden](grant numbers: CAN 2013/469, and CAN 2009/1175), FORTE (grant number: 2014-1962), and the Cancer Society in Stockholm (grant number: 141092).

Authors have no financial disclosure or conflict of interest.

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Table 1. Characteristics of cancer patients diagnosed between 1991 and 2009.

Cancer sites	ICD7	Parents were identifiable			At least two siblings in a family		
		n. patients	*n.* deaths[a]	Median age at diagnosis	*n.* patients	*n.* deaths[a]	Median age at diagnosis
Stomach	**151**	3 788	2 334	59	2 993	1 826	58
Colorectal	**153-4**	23 928	7 538	60	18 329	5 699	59
Lung	**162-3**	16 972	12 394	60	13 114	9 521	60
Breast[b]	**170**	51 273	4 372	54	40 738	3 463	54
Ovarian[b]	**175**	6 377	2 425	55	5 008	1 882	54
Prostate[b]	**177**	41 383	3 028	63	31 709	2 264	63
Kidney	**180**	5 975	1 836	58	4 636	1 437	58
Bladder	**181**	9 021	1 249	60	6 881	921	60
Melanoma	**190**	16 929	1 219	51	13 562	959	50
Nervous system[c]	**193**	11 737	3 731	49	9 565	2 996	50
Non-Hodgkin's lymphoma	**200,202**	9 025	1 869	56	7 088	1 453	55
Leukemia[c]	**204-9**	6 959	1 763	57	5 469	1 369	56

a Cancer-specific death within 5 years of cancer diagnosis
b Sex-specific cancers
c Excluded childhood cancers (diagnosis at age 0-14 years)

Table 2. Hazard ratios of cancer-specific death for familial cancer patients compared to sporadic cancer patients within 5 years of cancer diagnosis.

Cancer sites	Parents affected			Siblings affected			familial		
	n. patients	*n.* death	HR & 95% C.I.[a]	*n.* patients	*n.* death	HR & 95% C.I.[a]	*n.* patients	*n.* death	HR & 95% C.I.[a]
Stomach	195	119	**0.82 (0.68-0.99)**	45	31	1.06 (0.74-1.51)	236	147	0.85 (0.72-1.01)
Colorectal	2 563	778	0.94 (0.87-1.01)	861	272	0.95 (0.84-1.07)	3 274	1000	0.93 (0.87-1.00)
Lung	1 156	860	0.99 (0.93-1.07)	625	481	1.04 (0.95-1.14)	1 745	1314	1.01 (0.96-1.07)
Breast[b]	4 974	403	0.93 (0.83-1.03)	3 062	223	**0.81 (0.71-0.93)**	7 681	599	**0.88 (0.81-0.96)**
Ovarian[b]	204	82	1.09 (0.88-1.36)	111	58	**1.44 (1.11-1.88)**	305	134	**1.20 (1.01-1.43)**
Prostate[b]	6 427	392	**0.81 (0.73-0.90)**	3 897	260	**0.83 (0.73-0.95)**	9 494	604	**0.82 (0.75-0.90)**
Kidney	170	53	0.87 (0.66-1.15)	71	24	0.88 (0.58-1.33)	233	75	0.89 (0.70-1.12)
Bladder	417	46	0.79 (0.59-1.07)	129	16	0.84 (0.51-1.39)	535	62	0.81 (0.63-1.05)
Melanoma	583	28	0.72 (0.49-1.04)	402	34	1.06 (0.75-1.50)	947	60	0.88 (0.68-1.14)
Nervous system[c]	251	93	**1.26 (1.02-1.55)**	154	53	1.22 (0.93-1.60)	392	142	**1.24 (1.05-1.47)**
Non-Hodgkin's lymphoma	205	42	0.94 (0.69-1.28)	88	25	1.23 (0.83-1.83)	291	66	1.02 (0.80-1.31)
Leukemia[c]	206	40	**0.71 (0.52-0.98)**	84	17	0.69 (0.43-1.11)	286	56	**0.70 (0.54-0.92)**

a Hazard ratio (HR) with 95% confidence interval (C.I.) from Cox regression model adjusting for sex, age at diagnosis, year of diagnosis, socioeconomic status and region of cancer diagnosis.
b Sex-specific cancers
c Excluded childhood cancers (diagnosis at age 0-14 years)

Table 3. Hazard ratios of cancer-specific death for familial cancer patients compared to sporadic cancer patients within 5 years of cancer diagnosis, stratified by affected relative and by age.

	Parents affected			Siblings affected			familial		
Cancer sites	*n.* patients	*n.* death	HR & 95% C.I.[a]	*n.* patients	*n.* death	HR & 95% C.I.[a]	*n.* patients	*n.* death	HR & 95% C.I.[a]
Stomach									
< median age at dx	89	53	0.97 (0.73-1.28)	19	13	0.87 (0.50-1.51)	110	68	0.97 (0.76-1.24)
≥ median age at dx	106	66	**0.73 (0.57-0.94)**	26	18	1.22 (0.76-1.95)	126	79	**0.77 (0.61-0.98)**
Breast[b]									
< median age at dx	2 638	250	0.94 (0.82-1.07)	1 250	105	**0.78 (0.64-0.95)**	3 710	336	**0.87 (0.77-0.98)**
≥ median age at dx	2 336	153	0.90 (0.76-1.06)	1 812	118	0.85 (0.71-1.03)	3 971	263	0.89 (0.78-1.01)
Ovarian[b]									
< median age at dx	118	48	1.29 (0.97-1.73)	61	33	**1.75 (1.23-2.49)**	178	80	**1.44 (1.14-1.81)**
≥ median age at dx	86	34	0.90 (0.64-1.27)	50	25	1.17 (0.79-1.74)	127	54	0.97 (0.74-1.28)
Prostate[b]									
< median age at dx	3 552	228	**0.80 (0.70-0.92)**	1 815	131	**0.79 (0.65-0.94)**	4 883	327	**0.79 (0.70-0.90)**
≥ median age at dx	2 875	164	**0.84 (0.71-0.98)**	2 082	129	0.88 (0.74-1.06)	4 611	277	**0.86 (0.76-0.98)**
Nervous system[c]									
< median age at dx	131	36	**1.53 (1.10-2.14)**	60	11	0.79 (0.43-1.43)	180	49	1.32 (0.99-1.75)
≥ median age at dx	135	59	1.13 (0.87-1.47)	94	42	**1.42 (1.05-1.93)**	212	93	1.20 (0.97-1.48)
Leukemia[c]									
< median age at dx	93	15	**0.54 (0.32-0.92)**	25	6	0.88 (0.39-1.99)	120	21	**0.58 (0.37-0.91)**
≥ median age at dx	113	25	0.85 (0.57-1.28)	59	11	0.62 (0.34-1.13)	166	35	0.79 (0.56-1.11)

a Hazard ratio (HR) with 95% confidence interval (C.I.) from Cox regression model adjusting for sex, age at diagnosis, year of diagnosis, socioeconomic status and region of cancer diagnosis.
b Sex-specific cancers
c Excluded childhood cancers (diagnosis at age 0-14 years)

Table 4. Overall 5-year mortality rate and distribution of histology by family cancer history among patients diagnosed with cancer between 1993 and 2009.

Cancer sites	histology	*n.*patients	*n.*deaths	5-year mortality rate per 1000 person-years	n.patients				
					sporadic	(%)	familial	(%)	*P* [a]
Stomach	all	3459	2188	367.9 (352.8-383.6)					
	Adenocarcinoma	2613	1705	415.2 (395.9-435.4)	2434	(75.3)	179	(79.6)	
	Signet-ring cell carcinoma	441	342	497.3 (447.3-552.9)	412	(12.7)	29	(12.9)	
	Others	405	141	122.3 (103.7-144.3)	388	(12.0)	17	(7.6)	0.13
Breast[b]	all	47945	3951	19.8 (19.2-20.4)					
	Tubular	2557	41	3.5 (2.6-4.7)	2157	(5.3)	400	(5.6)	
	Ductal	32510	2609	19.5 (18.7-20.2)	27723	(67.9)	4787	(67.3)	
	Lobular	6240	389	14.7 (13.3-16.2)	5240	(12.8)	1000	(14.1)	*
	Others	6638	912	24.2 (22.7-25.8)	5708	(14.0)	930	(13.1)	**0.01**
Ovarian[b]	all	5884	2233	114.8 (110.1-119.7)					
	Serous	2579	1167	144.3 (136.2-152.8)	2425	(43.3)	154	(54.8)	*
	Mucinous	539	158	85.7 (73.3-100.2)	523	(9.3)	16	(5.7)	
	Endometrioid	732	195	70.8 (61.5-81.5)	694	(12.4)	38	(13.5)	
	Clear-cell	328	104	90.9 (75.0-110.2)	315	(5.6)	13	(4.6)	
	Adenocarcinoma NOS	899	393	143.0 (129.5-157.9)	868	(15.5)	31	(11.0)	
	Others	807	216	75.2 (65.8-85.9)	778	(13.9)	29	(10.3)	**0.002**
Prostate[b]	all	41118	2927	19.1 (18.4-19.8)					
	Adenocarcinoma	41017	2882	18.8 (18.1-19.5)	31602	(99.7)	9415	(99.8)	
	Others	101	45	191.5 (143.0-256.5)	83	(0.3)	18	(0.2)	0.27
Nervous system[c]	all	10881	3489	100.4 (97.1-103.8)					
	Astrocytic	3856	2869	436.7 (421.0-452.9)	3721	(35.4)	135	(37.3)	
	Oligodendroglial tumours and mixed gliomas	585	198	104.6 (91.0-120.2)	570	(5.4)	15	(4.1)	
	Ependymal	323	33	24.9 (17.7-35.1)	316	(3.0)	7	(1.9)	
	Glomas of uncertain origin	239	160	337.0 (288.6-393.5)	231	(2.2)	8	(2.2)	
	Medulloblastoma	111	52	157.8 (120.2-207.0)	106	(1.0)	5	(1.4)	
	Meningioma	3237	6	0.4 (0.2-1.0)	3129	(29.7)	108	(29.8)	
	Neurioma	1370	2	0.3 (0.08-1.3)	1325	(12.6)	45	(12.4)	
	Others	1160	169	38.9 (33.5-45.3)	1121	(10.7)	39	(10.8)	0.86
Leukemia[c]	all	6636	1618	72.5 (69.1-76.2)					
	Lymphatic	2688	431	43.3 (39.4-47.6)	2541	(39.9)	147	(54.0)	*
	Myeloid	2304	974	147.5 (138.6-157.1)	2246	(35.3)	58	(21.3)	*
	Monocytic	135	84	312.5 (252.3-387.0)	134	(2.1)	1	(0.4)	
	Others	1509	129	23.5 (19.8-27.9)	1443	(22.7)	66	(24.3)	**<0.001**

a Chi-square test for difference in proportions between familial cancer patients and sporadic cancer patients
b Sex-specific cancers
c Excluded childhood cancers (diagnosis at age 0-14 years)
* Histological type where difference occurred between familial cancer patients and sporadic cancer patients

Table 5. Histology-specific hazard ratios of cancer-specific death for familial cancer patients compared to sporadic cancer patients within 5 years of cancer diagnosis.

Cancer sites	histology	*n.*deaths sporadic	familial	HR & (95% C.I.) [a]
Stomach	Adenocarcinoma	1590	115	**0.80 (0.66-0.96)**
	Signet-ring cell carcinoma	319	23	1.48 (0.93-2.36)
	Others	137	4	0.52 (0.19-1.46)
Breast[b]	Tubular	37	4	0.61 (0.22-1.73)
	Ductal	2266	343	**0.86 (0.76-0.96)**
	Lobular	328	61	0.99 (0.75-1.30)
	Others	790	122	0.92 (0.76-1.12)
Ovarian[b]	Serous	1095	72	1.06 (0.83-1.34)
	Mucinous	147	11	**2.09 (1.09-3.98)**
	Endometrioid	186	9	0.99 (0.50-1.97)
	Clear-cell	100	4	1.05 (0.37-3.02)
	Adenocarcinoma NOS	381	12	0.80 (0.44-1.45)
	Others	205	11	1.36 (0.73-2.52)
Prostate[b]	Adenocarcinoma	2304	578	**0.83 (0.76-0.91)**
	Others	37	8	1.13 (0.49-2.60)
Nervous system[c]	Astrocytic	2764	105	1.09 (0.90-1.33)
	Oligodendroglial tumours and mixed gliomas	193	5	0.75 (0.30-1.86)
	Ependymal	32	1	2.09 (0.24-18.28)
	Glomas of uncertain origin	153	7	**2.78 (1.16-6.65)**
	Medulloblastoma	49	3	1.09 (0.28-4.30)
	Meningioma	6	0	-
	Neurioma	2	0	-
	Others	159	10	**2.35 (1.12-4.93)**
Leukemia[c]	Lymphatic	409	22	0.94 (0.61-1.45)
	Myeloid	951	23	0.92 (0.61-1.39)
	Monocytic	84	0	-
	Others	122	7	1.31 (0.60-2.86)

a Hazard ratio (HR) with 95% confidence interval (C.I.) is from Cox regression model adjusting for sex, age at diagnosis, year of diagnosis, socioeconomic status and region of cancer diagnosis.
b Sex-specific cancers
c Excluded childhood cancers (diagnosis at age 0-14 years)

Table 6. Observed counts of familial cancer patients and sporadic cancer patients stratified by tumor size/extent (T), lymph nodal involvement (N) and metastatic (M) status or FIGO categories between 2004 and 2009. Odds ratio (OR) and associated 95% Confidence Intervals (C.I.) for familial cancer patients vs. sporadic cancer patients are adjusted for sex, age at diagnosis, year of diagnosis, socioeconomic status and region of cancer diagnosis.

Cancer sites by TNM		**T1**	**T2-T4**	*P* [a]	**N-**	**N+**	*P* [a]	**M-**	**M+**	*P* [a]
Stomach	Sporadic / Familial	98/8	940/61	0.56	372/26	648/47	0.98	633/41	427/28	1
	OR & 95% C.I.		0.77(0.36-1.68)			0.92 (0.55-1.54)			1.05 (0.63-1.73)	
Breast	Sporadic / Famiial	8613/1495	5169/831	0.10	11418/1922	3763/661	0.40	11922/2000	316/53	1
	OR & 95% C.I.		0.94(0.85-1.03)			1.04 (0.95-1.15)			1.02 (0.76-1.37)	
Prostate	Sporadic / Familial	11220/3418	9373/2633	**0.006**	2398/706	426/115	0.48	4519/1294	1098/280	0.13
	OR & 95% C.I.		0.95 (0.90-1.01) [b]			0.90 (0.72-1.13)			0.89 (0.77-1.03)	
Cancer site by FIGO		**I**	**II-IV**							
Ovarian	Sporadic/ Familial	565/13	1268/74	**0.002**						
	OR & 95% C.I.		**2.70 (1.46-4.97)** [c]							

a Chi-square test for difference in proportions between familial cancer patients and sporadic cancer patients

b OR=0.89 (95% CI = 0.81 to 0.97) for T3 *vs* T1

c OR=2.79 (95% CI = 1.21 to 6.40) for FIGO Stage II, OR=2.52 (95% CI=1.33 to 4.79), for FIGO Stage III, OR= 3.22 (95% CI = 1.52 to 6.79) for FIGO Stage IV comparing to the lowest FIGO Stage I

Supplementary Table 1. Observed counts of familial breast cancer patients and sporadic cancer patients stratified by tumor size/extent (T), lymph nodal involvement (N) and metastatic (M) status between 2004 and 2009. Odds ratio (OR) and associated 95% confidence intervals (C.I.) for familial cancer patients vs. sporadic cancer patients are adjusted for sex, age at diagnosis, year of diagnosis, socioeconomic status and region of cancer diagnosis.

Cancer sites by TNM		**T1**	**T2-T4**	*P* [a]	**N-**	**N+**	*P* [a]	**M-**	**M+**	*P* [a]
Breast	Sporadic / Famiial	8613/ 1495	5169 / 831	0.10	11418 / 1922	3763 / 661	0.40	11922 / 2000	316 / 53	1
	OR & 95% C.I.		0.94 (0.85-1.03)			1.04 (0.95-1.15)			1.02 (0.76-1.37)	
Ductal	Sporadic / Familial	6468/ 1140	3639 / 555	**0.01**	8271 / 1397	2837 / 468	0.68	8783 / 1450	177 / 30	0.90
	OR & 95% C.I.		**0.88 (0.78-0.98)**			0.97 (0.86-1.09)			1.04 (0.70-1.54)	
Lobular	Sporadic / Famiial	987 / 163	815 / 168	0.06	1448 / 259	489 / 104	0.17	1501 / 295	51 / 11	0.78
	OR & 95% C.I.		1.26 (0.99-1.60)			**1.33 (1.02-1.73)**			1.21 (0.61-2.38)	

a Chi-square test for difference in proportions between familial cancer patients and sporadic cancer patients

Supplementary Table 2. Overall and stratified (by histology) hazard ratios of cancer-specific death within 5 years of diagnosis and using all available follow-up 1993-2010.

Cancer Sites	Histology	5-year follow-up n.deaths / n.patients		HR & (95% C.I.) [b]	All available follow-up n.deaths / n.patients		HR & (95% C.I.) [b]
		sporadic	familial		sporadic	familial	
Breast	All [a]	3433 / 41173	535 / 7187	**0.88 (0.80-0.96)**	5324 / 41173	871 / 7187	**0.91 (0.84-0.97)**
	Tubular	37 / 2157	4 / 400	0.61 (0.22-1.73)	113 / 2157	16 / 400	0.75 (0.44-1.27)
	Ductal	2266 / 27723	343 / 4787	**0.86 (0.76-0.96)**	3444 / 27723	563 / 4787	**0.91 (0.83-0.99)**
	Lobular	328 / 5240	61 / 1000	0.99 (0.75-1.30)	633 / 5240	124 / 1000	1.05 (0.86-1.27)
	Others	790 / 5708	122 / 930	0.92 (0.76-1.12)	1122 / 5708	163 / 930	0.85 (0.72-1.001)
Prostate	All [a]	2341 / 31685	586 / 9433	**0.83 (0.76-0.91)**	3192 / 31685	821 / 9433	**0.84 (0.78-0.91)**
	Adenocarcinoma	2304 / 31602	578 / 9415	**0.83 (0.76-0.91)**	3152 / 31602	813 / 9415	**0.84 (0.78-0.91)**
	Others	37 / 83	8 /18	1.13 (0.49-2.60)	40 / 83	8 / 18	0.89 (0.39-2.03)

a Note that hazard ratios may differ slightly from those on Table 2, which included patients from 1991.

b Hazard ratio (HR) with 95% confidence interval (C.I.) from Cox regression model adjusting for age at diagnosis, year of diagnosis, socioeconomic status and region of cancer diagnosis.